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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/551,840

01/20/2006

Fabrizio Samaritani

7541-6

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04/20/2009

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111 MONUMENT CIRCLE, SUITE 3700  
INDIANAPOLIS, IN 46204-5137

EXAMINER

GUPTA, ANISH

ART UNIT

PAPER NUMBER

1654

MAIL DATE

DELIVERY MODE

04/20/2009

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Advisory Action</b> <b>Before the Filing of an Appeal Brief</b>	<b>Application No.</b> 10/551,840	<b>Applicant(s)</b> SAMARITANI ET AL.	
	<b>Examiner</b> ANISH GUPTA	<b>Art Unit</b> 1654	

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 24 December 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.  
 b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on \_\_\_\_\_. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

#### AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because  
 (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);  
 (b) ☐ They raise the issue of new matter (see NOTE below);  
 (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or  
 (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).  
 5. ☐ Applicant's reply has overcome the following rejection(s): \_\_\_\_\_.  
 6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).  
 7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.  
 The status of the claim(s) is (or will be) as follows:  
 Claim(s) allowed: \_\_\_\_\_.  
 Claim(s) objected to: \_\_\_\_\_.  
 Claim(s) rejected: 46-49, 51-53, 57-63, 72-80, 82-193, 195-201, 203-215 and newly added claims 216-217.  
 Claim(s) withdrawn from consideration: \_\_\_\_\_.

#### AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).  
 9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).  
 10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

#### REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:  
See Continuation Sheet.  
 12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). \_\_\_\_\_.  
 13. ☐ Other: \_\_\_\_\_.

/Anish Gupta/  
 Primary Examiner, Art Unit 1654

Continuation of 11. does NOT place the application in condition for allowance because: For the rejection under Hoffman et al. (US2002/0165146), Applicants argue rejection based on Hoffman et al. is flawed because it is inappropriate to point to Hoffman and suggest that it teaches the use of any of a long list of possible excipients, when Hoffman stands for the proposition that the selection for excipients, e.g. the specific preservative claimed in Hoffman, is not predictable and in fact can form the basis for patentability. Applicants argue that Hoffman disclose a "laundry list of a broad range of possible constituents, including preservatives, isotonicity agents, buffers, antioxidants, and preservative enhancers." Applicants state that Hoffman recognizes the difficulty in preparing stable protein formulations. Applicants state that Hoffman does not include any working examples which contain excipients other than preservative and buffers. Applicants agree that given the teachings of Skrabanja for preparing stable FSH formulations, "it must be concluded that a person of ordinary skill in the art would not understand Hoffman as teaching the viability of each of the vast number of combination of constituents which could be theorized from the Hoffman disclosure." Applicants assert that their formulations all contain components having an active purpose and all formulations are stable. Referring to claims 212-213 Applicants state that "the subject matter of claim 212, 213 and 217 encompass basic and novel characteristics in that a pharmaceutical solution of FSH is provided which fulfills all the requirements for safe and effective use, while avoiding the inclusion of excessive number of components which could adversely impact stability and potency."

Applicants arguments have been fully considered but have not been found persuasive.

As in the previous office action, Applicants once again argue that Hoffman, "it must be concluded that a person of ordinary skill in the art would not understand Hoffman as teaching the viability of each of the vast number of combination of constituents which could be theorized from the Hoffman disclosure." Again it is asserted, that "[w]hen the reference relied on expressly anticipates or makes obvious all of the elements

of the claimed invention, the reference is presumed to be operable. . . . A prior art reference provides an enabling disclosure and thus anticipates a claimed invention if the reference describes the claimed invention in sufficient detail to enable a person of ordinary skill in the art to carry out the claimed invention; "proof of efficacy is not required for a prior art reference to be enabling for purposes of anticipation." See MPEP 2121. Applicants still have not provided any evidence that the disclosure of Hoffman is a non-enabling disclosure and one would be burdened with undue experimentation to make formulations using Hoffman's disclosure. The reference of Skrabanja et al. does not support the position for non-enablement since it does state that certain formulations, as disclosed in Hoffman, could not be formulated into stable formulations. Furthermore, Applicants have noted that Hoffman et al. "itself recognizes the difficulties of preparing stable protein formulations." Hoffman, knowing these difficulties, would not disclose components to be used in the formulations that would not lead to stable protein formulations. One of ordinary skill in the art reading Hoffman would recognize that each of the components disclosed could be used in a FSH formulations since that Hoffman et al. "itself recognizes the difficulties of preparing stable protein formulations."

Applicants have argued that Hoffman does not provide any working examples. However, as stated in the previous office action, lack of working examples is never the sole reason for questioning enablement. See MPEP 2164.01(c). Furthermore, the MPEP states "[c]ompliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." As support for the contentions that working examples are not necessary, attention is directed to Applicants claim 46, which allows for a "diluent." The instant specification states diluents include aqueous solven systemts which "may consist of water plus one or more miscible solvents, and may contain dissolved solutes such as sugars, buffers, salts or other excipients. The more commonly used non-aqueous solvents are the short-chain organic alcohols, such as, methanol, ethanol, propanol, short-chain ketones, such as acetone, and poly alcohols, such as glycerol." Looking to the specification, there are no working examples that contain a aqueous solution containing glycerol or short chain ketones. Applicants would not acquiesce to an enablement rejection based solely on the lack of working examples regarding the broadest reasonable interpretation of diluent for the claims.

Applicants argue that Hoffman disclose a laundry list of different components to make the FSH formulations. However, Hoffman describes the purpose for each additive utilized in the formulation. For example, for the preservative Hoffman states Preservatives, in one aspect, prevent or minimize deleterious microbial contamination in the formulation (see paragraph [0005]). An "isotonicity agent" is a compound that is physiologically tolerated and imparts a suitable tonicity to a formulation to prevent the net flow of water across cell membranes that are in contact with the formulation (see paragraph [0046]). The use of poloxamer 188 is used to reduce aggregation. These additives are particularly useful if a pump or plastic container is used to administer the formulation. The presence of pharmaceutically acceptable surfactant mitigates the propensity for the protein to aggregate (see paragraph [0100]). Thus, reading Hoffman as a whole one of ordinary skill in the art would have motivation to pick the different agents disclosed for a particular reason. Thus, the application of Hoffman in the obviousness rejection not based solely on the "fact that a claimed species or subgenus is encompassed by a prior art genus." So long as the prior art provides motivation and a reasonable expectation of success the reference renders obvious the claimed invention. Here the prior art does both.

The rejection is maintained.

For the rejection of under Hoffman et al. (US2002/0165146) in view of Skrabanja et al. Applicants argue Skrabanja et al. cannot be combined with Hoffman et al., the combination would not yield the present invention, and nothing in the references suggest stability and potency of LH or FSH/LH when combined with the preservatives of Hoffman. Applicants argue that Skrabanja et al. describes the difficulty of preparing stable protein solutions. Thus, Applicants state, "Skrabanja does not teach that FSH and LH can successfully be combined with other excipients, except to the extent of the formulation specifically described in Skrabanja."

Applicants state that "[i]t seems evident that Hoffman was not suggesting that LH could be combined in its FSH preparation, and that a

person skilled in the art reading Hoffman would understand it that way. Surely, if Hoffman et al. intended to disclose formulation including FSH and LH, they would have done so explicitly.”

Applicants also argue that there is no expectation of success in combining the two references. Applicants assert that neither reference clearly establishes that when FSH combined with LH in the Hoffman formulation, the formulation would be stable. Applicants refer again to portions of Hoffman et al. which deal with stability (specifically the discussion about cresol ) to argue that Hoffman discloses the difficulties with stabilizing FSH. Applicants state that Skrabanja does not disclose the use of preservatives.

Applicants arguments have been fully considered but have not been found persuasive.

First the rejection is based on Hoffman in view of Skrabanja. Hoffman was not used as the sole reference in establishing the obviousness rejection. Accordingly, the mere absence of the disclosure of LH in Hoffman is not dispositive for obviousness. The fact remains that Hoffman disclose that FSH can be used alone or in combination with other gonadotropins (see paragraph [0028]). Thus, from a stand point of obviousness, the question raised is why would one of ordinary skill in the art use LH in combination with FSH. ). It would have been obvious to use a combination of FSH and LH because the combination formulation has been used for stimulation of ovarian growth. This is the reason to combine the teachings of Hoffman et al. and Skrabanja et al.

With respect to Hoffman, aside from the preservative Applicants have not indicated what other components may lead to denaturing/instability of formulation. While Hoffman et al. may teach the problems associated with using preservatives such as m-cresol for other proteins it does not talk about other components. One cannot attribute the teachings for problems associated with preservatives to other component. Furthermore, while Hoffman et al. may teach the problems associated with using preservatives such as m-cresol the fact remains that for the FSH formulation, Hoffman teaches the use of the SAME preservatives which were discussed for denaturing other proteins. Thus, reading Hoffman would understand that while the preservative, m-cresol, has been reported to generally combine with and denature proteins (see paragraph [0005] of Hoffman) it would not denature an FSH formulation because Hoffman discloses and claims the use of m-cresol with FSH (see claims of Hoffman). Given the teachings of Hoffman and the fact that other gonadotropans can be used in the formulation, one would also expect that m-cresol would not denature leutinizing hormone.

Rejection is maintained.